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Functional State of the Microvascular Bed of the Skin in Essential Arterial Hypertension Assessed by Laser Doppler Flowmetry with Amplitude-Frequency Wavelet Analysis of Blood Flow Oscillations

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Abstract

Modern diagnostic technologies provide access to data which until recently were not available to specialists. Laser Doppler flowmetry (LDF) with amplitude-frequency wavelet analysis of tissue perfusion oscillations in patients with essential arterial hypertension (AH) revealed two completely opposite functional states of resistive precapillary arterioles. One group of patients (48%) had a significant increase in the sympathetic vascular tone component and vasomotor microvascular endothelial dysfunction (precapillary resistance). The second group of patients (52%), on the contrary, exhibited a significant reduction in myogenic tone accompanied by raised arterial blood inflow and increased blood filling of the venular microcirculatory bloodstream (postcapillary resistance). Since the main target of most pharmaceuticals is the resistive vessels, LDF can be useful for the selection of personalized antihypertensive therapy that considers the functional state of resistive microvessels.

Keywords: vasomotion, arteriole tone, peripheral vascular resistance, arterial hypertension, laser Doppler flowmetry, wavelet analysis

1. Introduction

In the past two decades, the interest in microcirculatory blood flow in patients with arterial hypertension (AH) has been steadily increasing due to the significant role of microcirculatory disorders in the pathogenesis of this disease [1–3] and unsatisfactory treatment results, when despite achievement of the target blood pressure with antihypertensive therapy, residual cardiovascular risks remain substantial [4]. Laser Doppler flowmetry (LDF) is a modern noninvasive technique for examining the microcirculatory blood flow in humans. Even though the skin vessels are not subjected to baroreflex regulation, the accumulated data suggests that the

microvascular bed of the skin may reflect the microcirculatory system state in other bodily organs and systems [5–8]. The results of functional LDF tests demonstrate a significant correlation between the left ventricular ejection fraction and the end-diastolic volume [9], flow-mediated vasodilation [10], and renal resistive index [11]. Discontinuation of antihypertensive therapy leads to a decrease in post-occlusive reactive hyperemia [12], which, in turn, correlates with the cardiovascular risk factors in the female population [13]. In 2011, the Peripheral Circulation Working Group of the European Society of Cardiology included LDF in the list of the recommended methods to study endothelial function [14].

Arterial hypertension is a hemodynamic disease with a blood pressure (BP) rise due to an increase in the cardiac output and/or peripheral vascular resistance [15]. In the classic work on normo-, hypo-, and hypertensive cats, Zweifach demonstrated that in the mesentery microvessels the greatest pressure gradient is recorded in arterioles $<50\ \mu\text{m}$ in diameter [16, 17]; at this level the Reynolds number is less than one and the viscous blood forces prevail over kinetic ones [18]. As in LDF resistive microvessels $<50\ \mu\text{m}$ in diameter are included in the probed volume [19], the interest in their functional state in AH is quite natural.

A fundamental feature of resistive arterioles is their high vasomotor activity. The arterioles are in constant motion, changing their tone and their lumen size, which manifests as vasomotions [20] with the respective changes in tissue perfusion. The vasomotion phenomenon is due to the ability of smooth muscle cells to spontaneously contract with an average frequency of 6 times per minute. It is the myogenic resistance at the capillary sphincter level that is the last blood flow control link before the exchange vessels, i.e. capillaries. Myogenic vasomotions are clearly conducted into the capillary bed of the human skin [21], and their amplitude is positively correlated with the number of functioning capillaries [22]. In arterioles, the basal tone and vasomotor activity of smooth muscle cells are modulated from the outer layer of the vessel wall by sympathetic nervous system 2–3 times per minute, and from the lumen by endothelial factors with a frequency of less than once per minute. The vascular tone-forming mechanisms (endothelial, neurogenic, and myogenic) act directly via the smooth muscle cells of microvessels and, as a result of periodic changes in blood flow resistance, generate the corresponding fluctuations in tissue perfusion [23, 24]. Due to the alternating contractions and relaxations of the smooth muscle in the arterioles and capillary sphincters, the arterial blood flowing into the capillaries is modulated to the optimal volume for transcapillary exchange [25–28]. During self-organization of microcirculation, all regulatory mechanisms interact with each other in positive and negative feedback loops that are aimed at maintaining tissue homeostasis. Thus, the tone-forming mechanisms function mainly at the resistive arteriole level, thereby determining not only the capillary hemodynamic parameters but also the peripheral vascular resistance (PVR).

Other microcirculation modulation mechanisms are passive in relation to the arteriolar smooth muscle cells, but they determine the blood filling volume of the microvascular bed (MVB) by changing the longitudinal pressure gradient caused by periodic changes in BP at the “inlet” (pulse BP) and pressure variation in the venules during the respiratory cycles at the “outlet” of MVB. The pulse oscillation amplitude reflects the condition of the inflow tracts (arterioles) and the arterial blood inflow into the MVB, and the amplitude of respiratory-associated blood flow oscillations characterizes the state of the capillary outflow tract, thereby reflecting the blood volume in the venular section of MVB [26, 29–31].

The main aim of this pilot study was to evaluate the functional state of resistive vessels of the skin in patients with essential arterial hypertension according by LDF with an amplitude-frequency wavelet analysis of microcirculation fluctuations.

2. Materials, methods and results

The skin perfusion was assessed in the supine position after a 15-min period of adaptation in a laboratory with a constant microclimate ($+23 \pm 1^\circ\text{C}$) in the morning (09:00–12:00 AM). The microcirculatory blood flow was recorded by a LAKK-02 single-channel laser analyzer of blood microcirculation in the visible red spectrum (wavelength of 630 nm) and a LAKK-TEST complex (OOO Research and Production Enterprise LAZMA, Russia) that allow evaluating the perfusion parameters in $\sim 1.0\text{--}1.5\text{ mm}^3$ of skin, at a constant temperature in the studied region of $+32^\circ\text{C}$. The sensor was located on the outer surface of the right forearm, in the midline 3–4 cm proximal to the wrist joint. The perfusion was recorded for 6 min. After the microcirculation study, all subjects received 24-h ambulatory blood pressure monitoring (ABPM) on the left shoulder.

The initial LDF recording (**Figure 1A**) was subjected to amplitude-frequency wavelet analysis. The time-averaged amplitude of vasomotions was estimated by the maximum values (A_{max}) in the corresponding [32, 33] blood flow modulation frequency range: endothelial (A_e)— $0.0095 - 0.021\text{ Hz}$; neurogenic (A_n)— $0.021 - 0.052\text{ Hz}$; myogenic (A_m)— $0.052 - 0.145\text{ Hz}$; respiratory-venular (A_v)— $0.145 - 0.6\text{ Hz}$; pulse-cardial (A_c)— $0.6 - 2\text{ Hz}$ (**Figure 1B**). The perfusion level (M) and the amplitudes of the blood flow modulation mechanisms were assessed in perfusion units (PU).

The functional activity of the tone-forming blood flow modulation mechanisms (endothelial, neurogenic, and myogenic) was evaluated as follows – the higher the vasomotion amplitude, the lower the tone, and vice versa, the lower the vasomotion amplitude, the higher the tone generated by this regulatory mechanism. If we take the zero amplitude as the longitudinal axis of a microvessel (LAV), and the maximum vasomotion amplitude as the vascular wall (**Figure 1B**), then the dependence of the microvessel lumen size on the vasomotion amplitude is clearly evident.

At the first stage of the study, the main objective was to assess the functional activity of resistive arterioles depending on the blood pressure level. At this stage, the subjects included 90 people (47 men and 43 women) divided into three groups. The control group (NT) consisted of 32 clinically healthy normotensive volunteers. The second group consisted of 32 patients with stage 1 essential AH (AH1). The third group included 26 patients with stage 2 AH (AH2). All patients with AH who were receiving antihypertensive therapy had their therapy discontinued 10–14 days prior to the study (washed out). In the rest of the patients, AH was newly diagnosed

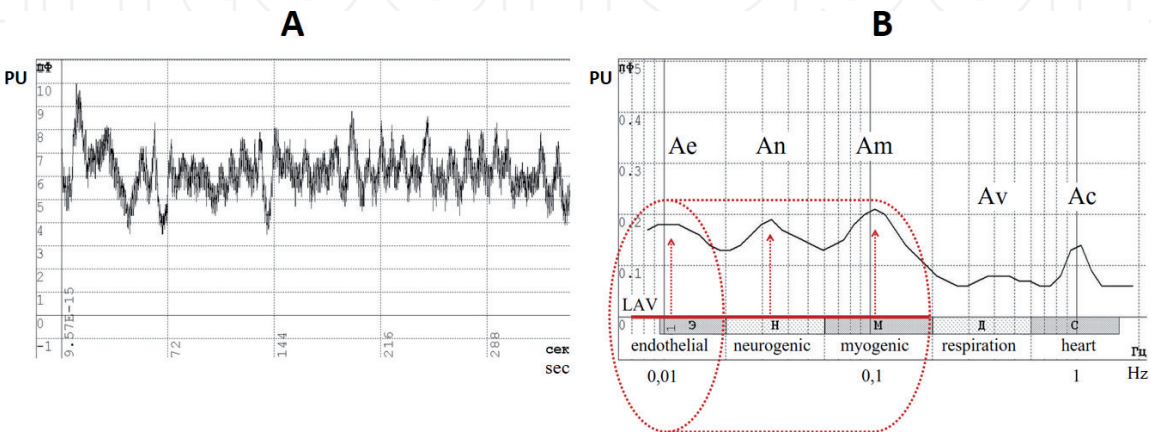


Figure 1. Laser Doppler flowmetry (LDF). (A) It is a perfusion characteristic during 6 min. (B) It is amplitude-frequency wavelet analysis of blood flow oscillations. Dotted lines indicate a microvessel, arrows mark the activity of tone forming mechanisms in blood flow modulation. LAV, the longitudinal axis of the vessel.

	NT (n = 32)	AH1 (n = 32)	AH2 (n = 26)
Age (years)	48.9 ± 10.4	48.7 ± 11.2	49.8 ± 10.8
Sex (men/women)	13/19	17/15	17/9
primary/washed	– / –	20/12	9/17
SBP (mmHg)	117.5 ± 9.8	141.5 ± 12.8 [*]	156.0 ± 15.4 ^{*,#}
DBP (mmHg)	74.5 ± 8.6	86.8 ± 9.8 [*]	95.2 ± 12.3 ^{*,#}
HR (beats/min)	65.6 ± 6.9	68.2 ± 8.1	70.6 ± 9.3

^{*}Differences are significant with respect to NT ($p < 0.000001$).
[#]Differences are significant with respect to AH1 ($p < 0.0001$).

Table 1.
The main characteristics of the analyzed groups—first stage of the study.

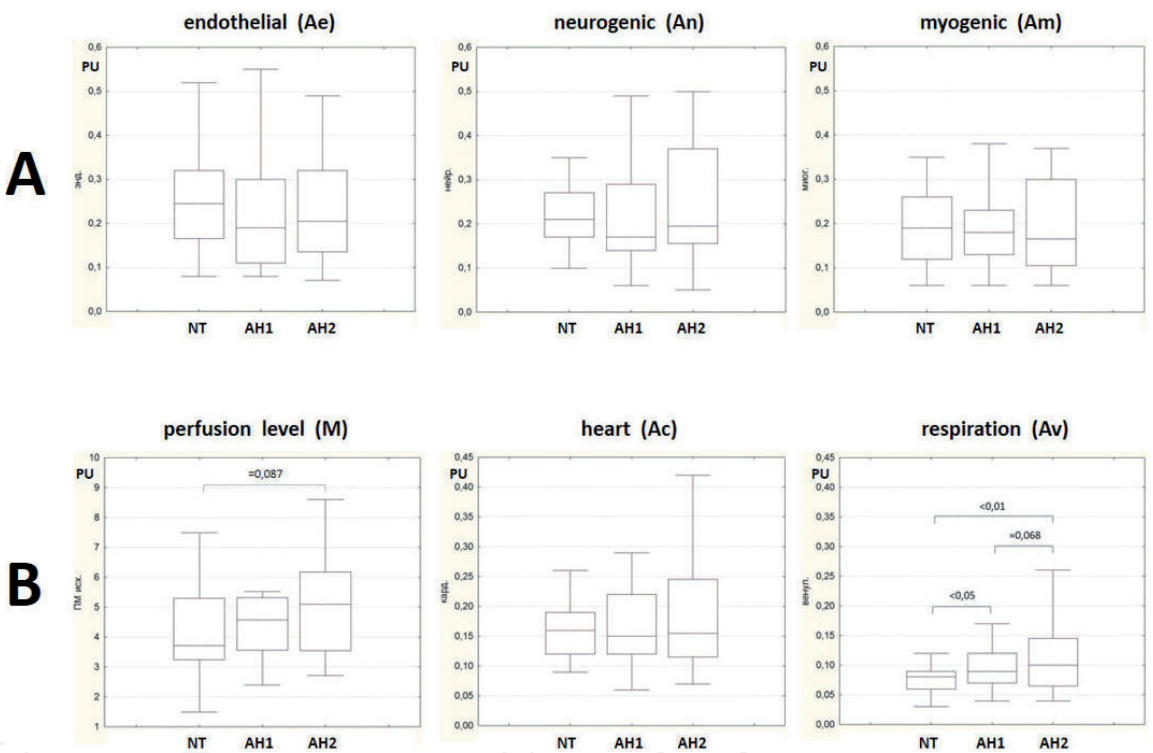


Figure 2.
LDF with amplitude-frequency wavelet analysis of blood flow in the first stage of the study. (A) The functional activity of tone-forming mechanisms (Ae, An, Am) of blood flow modulation. (B) The tissue perfusion (M) and the functional activity of the passive blood flow modulation mechanisms that reflect the condition of the blood inflow tracts to the capillary bed (Ac) and the outflow (Av) tracts. The rectangle indicates a range of 25–75 percentiles, and the median is indicated by a line.

and they had not received any drug therapy before the inclusion in the study (primary). The main characteristics of the analyzed groups and the hemodynamic parameters at the 10th minute of the adaptation period before LDF are presented in **Table 1**. According to the ABPM, the mean blood pressure (MBP) in the daytime was 89.8 ± 7.8 mm Hg in NT, 101.3 ± 5.2 mm Hg in AH 1, and 112.5 ± 6.9 mmHg in AH 2.

The functional activity of the main tone-forming microcirculation modulation mechanisms is shown in **Figure 2A**. Neither the expected increase in the basal myocyte tone (Am), nor a rise in sympathetic activity (An), nor signs of microvascular endothelial vasomotor dysfunction (Ae) were observed in any of the groups.

Figure 2B presents the analysis results of the tissue perfusion (M) and passive blood flow modulation mechanisms (Ac and Av) that determine the blood filling

of the microvascular bed (MVB). The data obtained demonstrate that statistically significant differences are present only in blood volume in the venular section of the MVB (Av), which indicates a gradual increase in the venular blood volume as AH progresses. It is very important that out of all six parameters analyzed, only the amplitude of respiratory-associated blood flow oscillations (Av) had a weak but significant positive correlation with the MBP in the daytime ($r = 0.25$; $p = 0.035$) and night time ($r = 0.29$; $p = 0.013$). This correlation means that the more blood there is in the venular MVB, the higher the BP.

From the results obtained, it can be concluded that the functional state of the blood outflow tracts from the capillary bed plays a more significant role in the total peripheral vascular resistance (TPVR) than the functional state of resistive precapillary arterioles. The obtained data are in agreement with the opinion of Coulson et al. who distinguish two vascular resistance levels: the first is before the capillary plexus with an estimated contribution to TPVR of 67% according to the authors, and the second is after the capillary plexus with a contribution to TPVR of about 33% [34].

Functional disorders were dominant not in the blood inflow to the capillaries (resistive arterioles) but in the outflow system (venules), and that was a completely unexpected finding and does not fit into any of the existing AH development hypotheses (neurogenic, salt, membrane, etc.). It is also highly important that LDF demonstrated changes in tissue perfusion associated with respiratory movements of the chest in far from all AH patients.

And what is the nature of respiratory-associated tissue perfusion oscillations? The blood flow oscillations synchronous with breathing spread into microvessels from the capillary blood outflow side and are recorded in the venules. A mechanical passive transmission of respiratory intrathoracic pressure changes mediated by the venous system is discussed as their origin.

Normally, no respiratory-associated tissue perfusion oscillations are identified in LDF, regardless of the arterial blood volume flowing into the microcirculatory bloodstream. This is due to several factors. Firstly, the cross-sectional area and volume of the venular MVB significantly exceed the cross-sectional area and volume of the arteriolar MVB. Secondly, veins collapse. To maintain a round vein shape, a pressure of about 6–9 mmHg is required, and at lower values, the veins are ellipsoidal. With the same perimeter, the cross-sectional area of an ellipse is much smaller than that of a circle, so when the pressure increases from 0 to 6–9 mmHg, the capacity of the venous segment of the vascular bed increases substantially. Already at 10 mmHg, the increase in venous capacity is more than 60% of the maximum possible. Then the increase in the venous volume decelerates dramatically and is about 30% with a pressure rise from 10 to 80 mmHg [35].

How can intrathoracic pressure changes during respiration be conducted along the venous vasculature to the periphery, that is, to the postcapillary skin vessels? At low pressures, the collapsed venous walls will obviously dampen the retrograde respiratory wave propagation. Consequently, the propagation of the respiratory wave to the periphery can be observed only with fully expanded veins. Thus, the higher the blood volume in the venous bed, and hence the pressure in them, the better the respiratory waves are propagated to the periphery, and the higher is the Av amplitude. It is obvious that there is a certain critical Av value that reflects the degree of blood filling of the venous bed. During a long period of observation and measurements, the maximum Av value was found empirically to be 0.08 PU, which suggests that the veins are not yet fully expanded because the respiratory waves are not observed during the recording of tissue perfusion. At Av values of 0.09 PU, respiratory-associated oscillations of perfusion begin to appear in the LDF recording. These oscillations have a low amplitude and are not observed at every breath, which most likely depends on the volume and rate of respiratory movements.

	NT (n = 30)	VN (n = 30)	VP (n = 33)
Age (years)	44.9 ± 10.4	48.9 ± 10.3	47.8 ± 10.3
Sex (men/women)	15/15	17/13	17/16
primary/washed	– / –	12/18	11/22
SBP (mmHg)	118.0 ± 10.1	140.0 ± 14.1 [*]	142.6 ± 14.7 [*]
DBP (mmHg)	76.5 ± 9.0	88.3 ± 9.8 [*]	91.1 ± 8.9 [*]
HR (beats/min)	65.8 ± 8.5	68.1 ± 7.9	67.2 ± 9.1

^{*}Differences are significant with respect to NT ($p < 0.000005$).

Table 2.
The main characteristics of the analyzed groups—second stage of the study.

For the second stage of the study, a homogeneous group of 63 patients with AH was selected with mean daytime SBP of 140–159 mmHg according to ABPM and/or mean daily DBP of 90–99 mmHg. Just as at the first stage, all AH patients receiving antihypertensive therapy had their therapy discontinued 10–14 days prior to the study (washed out), or AH was diagnosed for the first time with no drug therapy before inclusion into the study (primary). The control group (NT) consisted of 30 clinically healthy normotensive volunteers. Based on the functional state of the venular microvessels (Av), the AH patients were divided into two groups. The first (VN) included 30 patients (48%) with no signs of an increased blood volume in the venular MVB ($Av \leq 0.08$ PU). The second group (VP) consisted of 33 patients (52%) with signs of hypervolemia in the blood outflow tracts from the capillary bed ($Av \geq 0.09$ PU) of varying severity. The groups characteristics and the hemodynamic parameters immediately before LDF (10th minute of the adaptation period) are presented in **Table 2**.

Based on the grouping parameter (Av) value, 8 subjects in the NT group (27%) had a moderate increase in blood volume in the venular MVB – $Av = 0.09$ PU ($n = 3$), $Av = 0.1$ PU ($n = 4$), $Av = 0.12$ PU ($n = 1$).

Figure 3 presents clinical examples of LDF in the groups analyzed. BP was measured 5 min before the start of LDF. **Figure 3B** shows that not every respiratory movement of a normotensive volunteer from the NT group is accompanied by a distinct change in tissue perfusion, and the main differences are observed in the amplitude of respiratory-associated blood flow oscillations. In a VP patient (**Figure 3D**), the differences are more pronounced not in amplitude but in the frequency of perfusion changes that coincide with the respiration frequency.

An analysis of the perfusion level and microcirculatory blood flow modulation mechanisms which determine the MVB blood filling demonstrated that in the VN group there was no statistically significant difference in tissue perfusion and pulse oscillation amplitude relative to NT, and the blood filling of venules is lower (**Figure 4A**). The situation is totally different in the VP group. A statistically significant rise in tissue perfusion relative to NT ($p < 0.0003$) can be explained by an increased contribution to the power of the signal reflected from red blood cells in the venular MVB. An unexpected finding was a significant increase in the amplitude of pulse oscillations relative to NT ($p < 0.004$), which indicates a higher arterial blood inflow to the exchange vessels. The obtained results demonstrate that the increase in the MVB perfusion is caused not only by a larger blood volume in the venular section (disrupted outflow) but also by an increased inflow of arterial blood.

An analysis of the functional activity of the tone-forming mechanisms demonstrated a significant ($p < 0.002$) decrease was also observed in the amplitude of

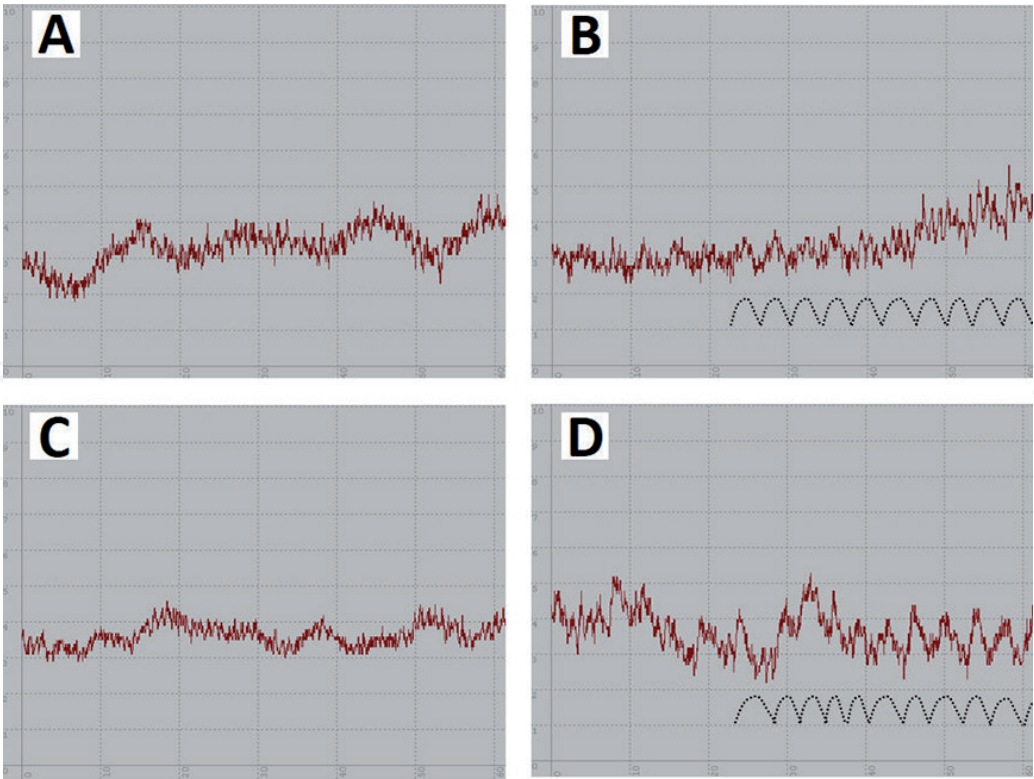


Figure 3.
The first minute of LDF. The functional state of the venular MVB. (A) NT group, BP is 115/70 mmHg: Respiratory-associated blood flow oscillations are not detected, perfusion (M) is 3.81 PU, respiration rate (RR) is 16/min, and Av is 0.05 PU. (B) NT group, BP is 130/80 mmHg: M – 3.82 PU, RR – 16/min, Av – 0.10 PU. (C) VN group, BP is 145/80 mmHg: M – 3.56 PU, RR – 16/min, Av – 0.07 PU. (D) VP group, BP is 150/90 mmHg: M – 3.89 PU, RR – 16/min, Av – 0.20 PU. The dotted lines reflect the changes in tissue perfusion synchronized with the respiratory chest movements.

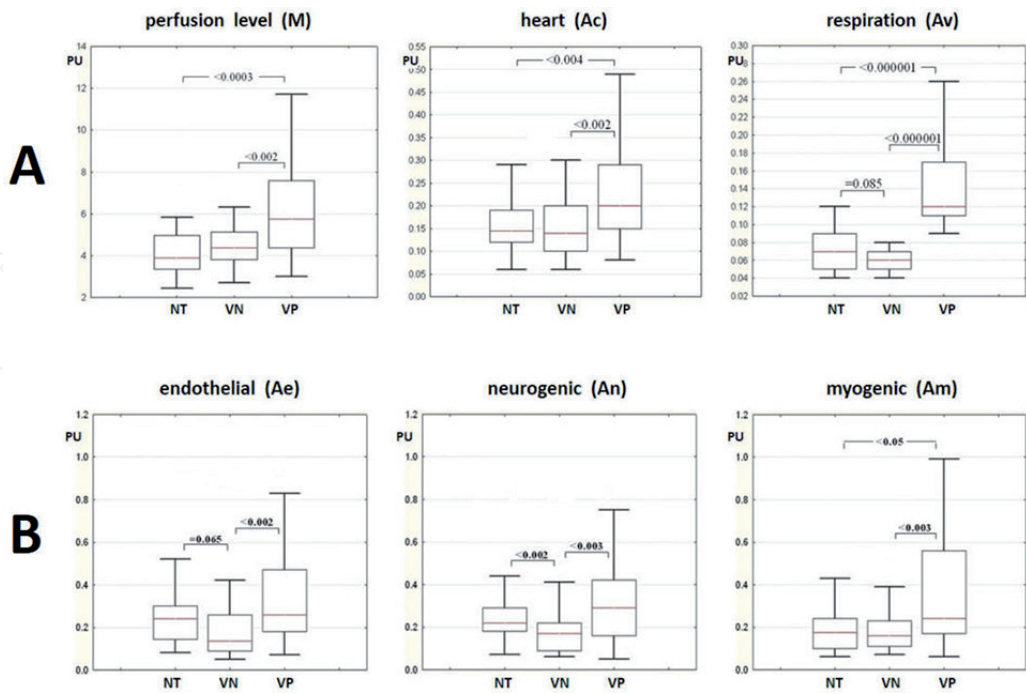


Figure 4.
LDF with amplitude-frequency wavelet analysis of blood flow in the second stage of the study. (A) The tissue perfusion (M) and the functional activity of the microcirculation modulation mechanisms which determine the blood filling of the microcirculatory bloodstream – The pulse (Ac) and respiratory-associated (Av) blood flow oscillation amplitude. (B) The functional activity of the tone-forming microcirculation modulation mechanisms (Ae, an, Am).

neurogenic vasomotions (An), which can be regarded as an increase in the sympathetic adrenergic tone. Meanwhile, the basal tone of smooth muscle cells (Am) was unchanged and comparable to that in the control group (**Figure 4B**).

The tone-forming mechanisms were in a completely opposite state in the VP group. Relative to NT, there were no significant differences in the functional activity of the endothelial and neurogenic arteriolar tone regulation mechanisms, although there was a trend towards a vasomotion amplitude increase by these regulatory mechanisms. However, the basal tone of the smooth muscle cells in precapillary arterioles and capillary sphincters was significantly reduced ($p < 0.05$), which was indicated by the myogenic vasomotion amplitude (Am) increase.

Thus, according to the functional state of the skin microcirculatory vessels, we obtained two completely opposite groups of patients with AH that initially seemed homogeneous. The differences between the groups were observed in all the six parameters analyzed: tissue perfusion ($p < 0.002$), amplitude of pulse ($p < 0.002$) and respiratory-associated ($p < 0.000001$) blood flow oscillations, amplitude of endothelial ($p < 0.002$), neurogenic ($p < 0.003$), and myogenic ($p < 0.003$) vasomotions.

From the data obtained it can be assumed that in AH patients without disruptions blood outflow from the capillary bed, hypertension is caused by an increase in the sympathetic adrenergic vascular tone regulation mechanism and by a vasomotor dysfunction of the microvascular endothelium. In patients with impaired blood outflow from the capillary bed associated with a decline in the myogenic tone of precapillary arterioles, an increase in the arterial blood inflow is observed.

The ABPM results were no less interesting. **Figure 5** shows significantly higher BP during both day and nighttime in the VP patients relative to VN, except for the nocturnal diastolic BP. A paradoxical situation arose – BP was higher in patients with a reduced resistive arteriolar tone than in patients with an increased tone.

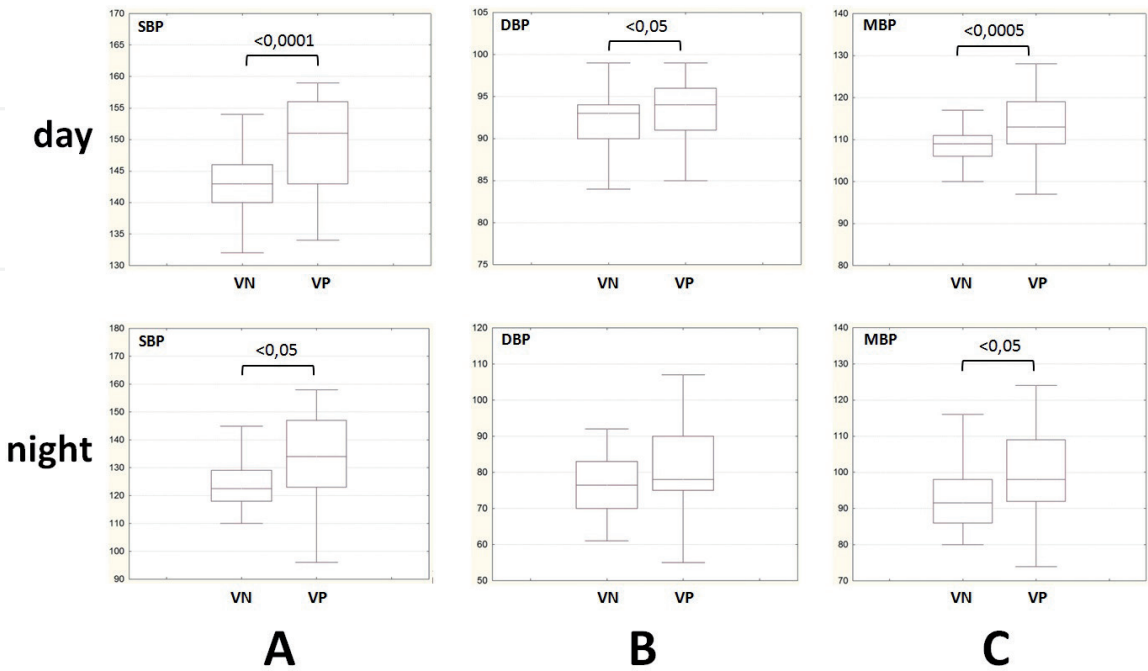


Figure 5.
The results of 24-h arterial blood pressure monitoring (ABPM). (A) Systolic BP (SBP). (B) Diastolic BP (DBP). (C) Mean BP (MBP).

3. Discussion

The pilot study of the functional state of the skin microvascular bed in essential arterial hypertension raised fundamental questions that require reflection and detailed consideration.

The first fundamental question is the validity of LDF in assessing the functional state of the resistive vascular bed in AH. On the one hand, there is no statistically significant correlation of BP with the functional activity of the tone-forming mechanisms in resistive arterioles. This can be explained by the absence of regulatory baroreflex mechanisms in the skin microvessels in contrast to microvessels in the striated muscle. On the other hand, the amplitude-frequency wavelet analysis of microcirculatory blood flow oscillations demonstrated that the functional state of the regulatory mechanisms in exchange microvessels may differ drastically in the initially homogeneous group of AH patients. This, in turn, not only has different hemodynamic and metabolic effects but quite evidently demands an individual approach to selecting antihypertensive therapy.

Let us consider the VN group in terms of the functional state of resistive arterioles. This group has a moderate decrease in the endothelial vasomotion amplitude with a trend towards significance ($p = 0.065$), indicating vasomotor dysfunction of the microvascular endothelium, which is consistent with the previously obtained results [36]. The group also exhibits a significant reduction in the neurogenic vasomotion amplitude ($p < 0.002$), which can be regarded as an increase in the sympathetic adrenergic tone. From the data obtained, it can be concluded that the functional state of resistive arterioles in AH patients with normal blood outflow from the capillary bed does not contradict Lang's neurogenic theory and the current ideas about the role of endothelial dysfunction in the AH pathogenesis. In such a functional state of the resistive arterioles, the prescription of drugs which lead to a tone decrease through various regulatory mechanisms can be considered quite justified.

Now let us consider the VP group, which raises many more questions. Based on the precapillary arteriole functional state, it can be concluded that there is a significant decrease in the basal tone of smooth muscle cells in arterioles and capillary sphincters. The insignificant (relative to NT) trend towards an amplitude increase (tone decline) of endothelial and neurogenic vasomotions can be explained in two ways: 1) changes in the regulatory systems themselves; 2) decreased smooth muscle cell sensitivity to the regulatory effects of the endothelium and the sympathetic adrenergic system. The hemodynamic consequences of the precapillary arteriolar tone are an increase in the arterial blood inflow (A_c), venular blood volume (A_v), and as a result, tissue hyperperfusion, i.e. an increase in M .

Gryglewska et al. [37] also draw attention to a significant increase in the vasomotion amplitude in the neurogenic and myogenic activity range in patients with masked hypertension. The patients analyzed in that study were on average 10 years younger than our subjects. The data presented by the authors demonstrate that a neurogenic tone decline is observed against the background of an increased norepinephrine level. One possible cause for the increased plasma norepinephrine is the neurotransmitter leakage from the neuro-muscular synapses in microvessels in AH patients when the sympathetic nervous system activity is enhanced. This phenomenon is well-established for skeletal muscles [38, 39], but not for the skin microvessels which are not subject to baroreflex regulation [40]. The authors of the study suggest that the vasomotion amplitude increase in patients with masked hypertension is of a compensatory nature, aimed at meeting the metabolic needs of tissues when there is a reduced number of functioning capillaries, while the

increase in blood pressure is due to the influence of various hormones, proinflammatory cytokines, and other humoral substances possibly secreted by the visceral adipose tissue [37].

Similar results for the functional state of the resistive skin microvessels in AH patients were also obtained also in another study [41]. In an age-matched group, Rossi et al. observed a significant increase in tissue perfusion compared to normotensive subjects, associated with significantly higher vasomotion amplitudes within the range of the endothelial, neurogenic, respiratory (venular), and cardiac blood flow modulation mechanisms. The authors explain the enhanced vasomotor function of the microvascular endothelium as a response to an increase in the shear stress at high BP values, and the higher vasomotion amplitude in the range of the neurogenic regulation mechanism as sympathetic nervous system activation. The authors consider the observed increase in the pulse oscillation amplitude a manifestation of a high BP level, and the rise in the respiratory-associated blood flow oscillation amplitude as a compensatory reaction aimed at extending the time for oxygen extraction by tissues under microvascular rarefaction.

Hemodynamic changes at the MVB level entail significant metabolic changes. Of the three main metabolic mechanisms (diffusion, filtration-reabsorption, and vesicular), filtration-reabsorption depends directly on the hemodynamic parameters. This metabolic mechanism is described by the Starling equation and provides bidirectional transendothelial transport of water-soluble and low-molecular-weight substances due to the difference in the hydrostatic and colloid osmotic blood pressures. Enhanced arterial blood inflow (A_c) with impaired venular outflow (A_v) in VP patients can lead to a substantial rise in hydrostatic pressure in the capillaries, which is observed in far from all AH patients during direct pressure measurement in the nail bed capillaries [42–44]. An increase in the capillary hydrostatic pressure leads to a shift in the filtration-reabsorption metabolic mechanism towards the predominance of filtration, with developing hyperhydration of the interstitial space and latent fluid retention in the tissues [45, 46]. The hyperhydration of the interstitial space increases the blood↔cell distance for nutrients and tissue metabolism products, leading to a disruption in the metabolic process rate.

Another very important issue is the choice of antihypertensive therapy in this group of patients. The choice of vasodilating drugs is highly dubious. An additional decline in the initially low resistive arteriolar tone can have a range of negative consequences, including orthostatic instability, syncope, peripheral edema, etc. The study by Makolkin et al. [47] is highly illustrative in this respect. The authors define several hemodynamic microcirculation types (normocirculatory, spastic, hyperemic, and congestive-stasical) and note the greatest effect of calcium antagonists in the spastic type, while these cause puffiness in the lower legs and feet, as well as hot flashes in the congestive-stasical type.

It can be speculated that patients in this group are poorly compliant with therapy due to low tolerability, or it is difficult to achieve the target BP. As Engholm et al. demonstrated in their study, in patients with a low systemic vascular resistance index (SVRI), additional administration of antihypertensive drugs from other groups (two-component therapy) significantly lowers BP without changing SVRI. There is also an insignificant trend towards an increase in the left atrial size with a decrease in the left ventricular stroke volume and cardiac index relative to patients with high SVRI [48]. Based on the functional state of the arteriolar and venular microvessels in the VP group, it can be assumed that in this case the prescription of drugs with venotonic and/or diuretic effects will be most justified.

The next important question is the reasons for such a substantial difference in the functional state of the skin microvessels, when all the parameters analyzed by LDF differ significantly. It can be assumed that this is due either to different

etiological factors or to the pathological process duration. The early AH development stages are not marked by elevated levels of endothelin, a marker of vasomotor endothelial dysfunction [49]. We were not able to assess the pathological process duration in the analyzed groups, which is one among many weaknesses of this pilot study, but it can be assumed, based on the significant reduction in the microvascular endothelial vasomotor function, that the pathological process had been developing longer in the VN patients.

The role of the temporal factor in the detected functional differences is supported by studies of vasomotor function of microvessels in different AH models in laboratory animals. Boegehold et al. demonstrated that a high-salt diet for 6–7 weeks in healthy four-week old rats resulted in a significantly higher amplitude of vasomotions in the mesenteric arterioles with a diameter of 30 μm compared to the control group that did not received the salt load [50]. In another study in 10–12 week-old spontaneously hypertensive rats (SHR), Noble et al. not only observed a significant rise in the vasomotion amplitude in the spinal skeletal muscle arterioles with a diameter of <30 μm relative to those in normotensive animals, but also a significant increase in the diameter of precapillary arterioles (6–15 μm) and postcapillary venules (15–40 μm) [51]. In another study of the cerebral microvasculature in SHR, a significant increase in the vasomotion amplitude was demonstrated in micro- and larger (diameter 30–70 μm) vessels, where the smooth muscle layer is more pronounced and the neurogenic (sympathetic adrenergic) vascular tone regulation mechanism predominates [52]. The obtained experimental results in laboratory animals are quite consistent with the functional state of microvessels in the VP group, which may indirectly indicate the initial manifestations of the pathology in this group of patients.

This hypothesis is also supported by the high correlation of Av with MBP obtained in the combined NT + VP group ($n = 63$): day time – $r = 0.66$ ($p < 0.0001$); night time – $r = 0.76$ ($p < 0.0001$). This relationship indicates that the progression of disorders in the venular-venous vascular bed is accompanied by an increase of BP. It can be hypothesized that first the renin-angiotensin system is activated to maintain tissue homeostasis and compensate the filtration-reabsorption imbalance, leading to an increase in the resistive arteriolar tone, which in turn leads to a decrease in hydrostatic blood pressure in the capillaries. This regulatory mechanism restores the filtration-reabsorption metabolic balance but triggers a vicious circle which ultimately leads to structural microvascular changes. Based on this hypothesis, it can be suggested that the VP patients are at the early AH stage (functional impairment stage), and the VN patients have a longer course of the pathological process with the development of structural changes. It is extremely difficult to determine the AH course duration since many patients do not feel elevated BP. In this study, in 23 patients (37%) from both groups AH was diagnosed incidentally without any previous suspicion on their part about the existence of a pathology.

Another important issue concerns the causes of disrupted blood outflow from the capillary bed, which may be due to several factors or their combination. One may be a disturbance in the functional state of the major veins which is observed both in laboratory animals [51] and in some AH patients and is expressed as a decrease in the venous wall elasticity with an elevation of their tone and the blood pressure in them [53–56]. Another cause may be an increase in the right atrial pressure, which is observed in some AH patients [57, 58].

Another highly important issue concerns the BP level. What causes a higher BP level in VP patients relative to the VN group? The venular microvessels are generally believed to contribute not more than 8–9% of the PVR [59], although, as noted above, the contribution of the postcapillary section may be much higher [34]. But here another factor should be considered that significantly affects BP, i.e. the

cardiac output. The cardiac output in AH patients may be elevated during venoconstriction [60]. Based on the significantly lower peripheral vascular resistance, the VP patients can be hypothesized to have a hyperkinetic circulation type, and their higher BP values are due to a combination of two factors – an increase in the cardiac output, as noted in other studies [48], and a disruption of the blood outflow from the capillary bed with an increase in PVR at the postcapillary (venular) level.

Regardless of the reasons for the hindered blood outflow from the capillary bed, the mechanism that increases the amplitude of myogenic vasomotions in the precapillary arterioles and capillary sphincters is baffling. Normally, in a closed cardiovascular system, an increase in the venous pressure results in a consecutive rise in the capillary and precapillary arteriolar pressure. The smooth muscle cells of the resistive microvessels respond to increased pressure and distension by contracting by the Ostroumov-Bayliss mechanism, which should lead to a rise in their tone with a decrease in the amplitude of myogenic vasomotions (A_m). But in the VP group, the exact opposite effect is observed. How can we explain it?

It can be hypothesized that the precapillary arteriolar tone decline is of a compensatory nature, aimed at overcoming the raised resistance at the postcapillary level. The increase in the arterial blood inflow is aimed at overcoming the impaired venous outflow. But from the metabolic expediency point of view, this compensation mechanism is extremely unfavorable. This can be assumed to be a consequence of the functional features of the smooth muscle cells in VP patients. Falcone et al. established *in vivo* that an increase in venous pressure in the cremaster muscle of SHR caused a more pronounced constriction reaction of the 15–100 μm arterioles than in normotensive animals [61]. Another research group demonstrated on mesenteric arterioles (diameter 100–150 μm) *in vitro* that in SHR the smooth muscle cells (lacking sympathetic innervation) develop a significantly higher vasomotion amplitude in response to norepinephrine compared to normotensive animals [62].

The results of this pilot study suggest that the contribution of the venular MVB to PVR is more substantial, and the generally accepted vascular resistance scale requires adjustment. In previous studies on healthy normotensive volunteers it was demonstrated that the blood volume in the skin venular microvessels has a positive correlation with BP, and a negative correlation not only with the magnitude of nocturnal BP decline, but also with the dilation response of MVB during the heat test, the nociception system activation, and post-occlusive reactive hyperemia [63, 64]. MVB is anatomically located between the arterial and venous systems, and, as capillaries do not stretch, the disruptions in the outflow system naturally affect the inflow system to the exchange vessels with all the logical metabolic consequences. This state can be formulated simply as “no outflow – no inflow”.

The venular MVB itself deserves special attention. What is the physiological underpinning of the significantly larger vascular volume in the venular MVB than on the arteriolar side? This is what Nature intended, and therefore there is a physiological reason. Unlike arterioles, which only regulate blood inflow to the capillaries, many important functions are performed at the venular level. One is that mast cells are located in the immediate vicinity of venules with a diameter of 40–80 μm . This protective system reacts to various chemical and biological noxious agents entering the systemic circulation and it is situated in the venular section of the MVB. Postcapillary venules provide the exchange of macromolecules and protein-bound substances in the bloodstream by vesicular transport. Recognition, immobilization, “unpacking” of transport molecules, and vesicle formation require some time and are facilitated by the hemodynamic conditions in the venular section of MVB, since it has the slowest blood flow in the entire cardiovascular system. The venular section occupies a strategic position and is the first to receive metabolic information.

In the conducted studies it was discovered that any changes in venous MVB affect the functional state of the adjoining afferent arteriole and the effects are observed up to 12 mm from the stimulus applied. The following was revealed: constriction reactions of arterioles to intravenular administration of norepinephrine [65], dilation reactions to acetylcholine [66], adenosine [67], ATP [68], dilator prostanoids [69], and even to the metabolic stimulator 2,4-dinitrophenol [70]. In response to an increase in shear stress, venular endothelium produces NO leading to a corresponding dilation of the adjoining arteriole [71]. There is an opinion that the arteriolar NO level is determined by its venular concentration, whose basal level is maintained by the secretory activity of the venular endothelium [72]. The endothelium of the venous bed is also sensitive to the blood gas composition. Tkachenko demonstrated that with blood O₂ saturation < 68% sympathetic stimulation leads to a contraction of the muscle veins (>100–150 μm), when O₂ is in the range of 68–85%, the reaction can be both constriction and dilatation, but at saturation values of >85%, sympathetic stimulation causes only venous dilation [73].

4. Conclusion

LDF is a relatively new technique for studying microcirculation in humans which is going through the stages of adoption, data accumulation, and interpretation of the obtained results. A review of the scientific literature over the past 20 years has identified only 143 studies of microcirculation in humans by LDF with wavelet analysis of blood flow oscillation. The total number of healthy subjects and patients with various organ and system diseases involved in the studies does not exceed 2600 [74].

The main aim of this pilot study was to evaluate the informativeness of LDF in assessing the functional state of the skin microvascular bed in patients with essential arterial hypertension. The study has many weaknesses, due to the retrospective data analysis and the inability to collect information on the central hemodynamic parameters and humoral status of the patients. Nevertheless, it can be concluded that the aim has been achieved. The obtained results are unexpected; however, they allow the microcirculatory blood flow problems in patients with AH to be viewed in an entirely new light.

Several quite precise conclusions can be made based on the study:

1. LDF is a very promising method to study the functional state of microcirculation in humans and can be useful for the selection of personalized antihypertensive therapy.
2. The functional activity of the tone-forming mechanisms (endothelial, neurogenic, myogenic) of the resistive arterioles in the skin is not correlated with BP according to ABPM data.
3. AH patients can differ significantly in their functional status of resistive microvessels. One half of the patients have an increased arteriolar tone without hemodynamic disruptions in the venular MVB. The other half of the patients is a complete opposite, that is, they exhibit a decrease in arteriolar tone associated with disrupted blood outflow from the capillaries. These functional differences must be considered when selecting antihypertensive therapy. This may assist in increasing the effectiveness of therapy and patient compliance with the treatment.

4. The role of the venular-venous vascular bed in AH is underestimated, and further studies in this area are required; this will contribute to solving many problems that cardiologists face today.

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Conflict of interest

The author declare no conflict of interests.

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